IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:

ATKINSON et al.

Serial No.: 09/523,923

Filed: March 9, 2000

Atty. File No.: 2265-12

For: PRODUCT AND METHOD FOR BIOLOGICAL ANCHORING OF CONNECTIVE TISSUE TO BONE

Group Art Unit: 1655

Examiner: Chakrabarti, A.

SUPPLEMENTAL RESPONSE AFTER FINAL REJECTION

#18
CD
5/21/02

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office at 703/8729307 on May 9, 2002

SHERIDAN ROSS P.C.

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Commissioner for Patents
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Dear Sir:

This Supplemental Response is filed in response to a final Office Action having a mailing date of June 26, 2001. An Amendment and Response that was fully responsive to the June 26 Office Action was filed on October 26, 2001, along with a request for a one-month extension of time. A Notice of Appeal, with the requisite fee and a request for an additional two-month extension of time was filed on December 20, 2001, which extended the time for responding from December 20, 2001 to February 20, 2002. Enclosed herewith is a request for a three-month extension of time to extend the time for responding from February 20, 2002, to May 20, 2002. Please debit Deposit Account No. 19-1970 for the requisite fee.

Please reconsider the above-identified patent application as follows.

REMARKS

Applicants would like to thank Examiner Chakrabarti and his supervisor, Examiner Zitomer, for the courtesy extended to Applicants' agent, Angela Dallas, during the personal interview on February 5, 2002. During the interview, the Examiners and Dr. Dallas discussed the rejections under 35 U.S.C. § 103. The Examiner suggested that a Supplemental Response or Declaration be filed which shows data in support of Applicants' position that the composition of the present invention induces a bone-cartilage-tendon interface at the site of repair. The Examiner indicated that this response would be considered after final without the need to file a Request for Continued Examination.

Rejections of the Claims Under 35 U.S.C. § 103:

The Examiner has maintained four rejections of the claims under 35 U.S.C. § 103, over various combinations of references, wherein Rodeo et al. is the primary reference. Applicants again traverse this rejection. Applicants position remains the same with regard to the various combinations of references and therefore, those detailed arguments will not be repeated in full here, but rather, are incorporated by reference to the response filed on October 26, 2001. Instead, Applicants will address the Examiner's concerns as discussed with Dr. Dallas during the February 5, 2002 interview.

Initially, Applicants reiterate that the present invention is directed to the discovery by the present inventors that a complex mixture of proteins, as claimed in the present claims, in combination with the recited matrix, is capable of inducing the formation of a bone-*fibrocartilage/calcified cartilage*-connective tissue interface *in vivo*. In other words, the claimed mixture is used for the repair or reattachment of a particular type of connective tissue (ligament, tendon, or cementum) to bone by forming a tissue that includes transition zones of fibrocartilage and calcified cartilage *between* the connective tissue and bone. The claimed mixture of proteins includes, minimally, transforming growth factor β1 (TGFβ1), bone morphogenetic protein (BMP)-2, bone morphogenetic protein (BMP)-3, and bone morphogenetic protein (BMP)-7, in the quantities recited in Claim 1. One such mixture meeting the limitations of the claims is referred to in the specification as Bone Protein (BP) (See, e.g., Table 5). It is again noted that the range of proteins claimed is not overly broad, but rather encompasses the range of the recited proteins determined for

an exemplary composition (i.e., BP). Other mixtures meeting the limitations of the claims are described in Examples 5-8.

Physiological bone induction requires stimulatory and inhibitory factors for bone induction. A composition comprising only a stimulator of bone induction (e.g., a single recombinant BMP or multiple stimulators, as described by prior investigators) may sub-optimally regenerate tissue at the bone-tendon interface (or meniscus/other tissues). Although compositions described by prior investigators might produce a *functional* attachment of tendon or ligament to bone, which may even include an attachment site having a progression from tendon or ligament to bone, the development of a physiologically natural connective tissue-to-bone attachment, which includes transition zones of fibrocartilage and calcified cartilage between the connective tissue and bone, has not been demonstrated using such compositions.

Examples 2, 3, and 4 of the present specification are *in vivo* experiments in which a composition meeting the limitations of the claims showed superior tendon-cartilage-bone growth. Applicants will describe the results of these experiments and then refer to Rodeo et al. to show how these results are superior to that demonstrated by Rodeo et al.

Referring to Example 2, a composition of the present invention was used to heal an attachment of the long digital extensor tendon to bone in rabbits. As compared to controls (matrix only or no treatment), the composition of the present invention showed newly formed bone in greater proximity to the tendon than either of the controls. Furthermore, areas treated with the composition contained fibrocartilage in close juxtaposition to the tendon, whereas the controls showed only fibrous tissue juxtaposed to the tendon (see pages 58-59).

Referring to Example 3 (see pages 59-63), a composition of the present invention was used to heal a semitendinosus tendon attachment to bone in an anterior cruciate ligament reconstruction surgery in rabbits. Results showed that, at two weeks, there was extensive formation of new bone trabeculae and cartilage in the tendon-bone interface. At four weeks, there was generally more cartilage in the tendon-bone interfaces in the specimens treated with the composition of the invention as compared to the controls, and the cartilage in the tendon-bone interfaces was more mature in the composition-treated specimens. Incorporation of the tendon with establishment of collagen fiber continuity between tendon and bone was often more advanced in the composition-treated specimen.

At 8 weeks, the composition-treated specimens demonstrated more cartilage and new bone formation around the tendon graft than in the controls. Mechanical testing further showed that the composition-treated attachments were significantly stronger than the controls.

Referring to Example 4 (see pages 64-66), a composition of the present invention was used to heal an attachment of infraspinatus tendon to bone in sheep. The results demonstrated that composition-treated sheep had a higher percentage of newly synthesized bone and cartilage as compared to the control.

Together, these experiments demonstrate that a composition of the present invention induces an effective attachment of tendon/ligament to bone, with the formation of new bone trabeculae and with the formation of significant fibrocartilage in close juxtaposition to the tendon. In other words, the composition of the present invention induces an attachment of this type of connective tissue to bone that is similar to the natural morphology of connective tissue to bone, which includes transition zones of fibrocartilage and calcified cartilage between the connective tissue and bone.

In contrast, compositions used to enhance the reattachment or repair of connective tissue to bone prior to the present invention have failed to induce the formation of such a natural morphology, and in particular, do not induce the preferred fibrocartilage and calcified cartilage transition zone. Turning to Rodeo et al., which is cited in all of the combinations of references under the § 103 rejections, Applicants respectfully refer the Examiner to the detailed discussion of this reference as set forth in the Amendment and Response filed on October 26, 2001 (see page 8 of the response). Briefly, Applicants referred the Examiner to portions of Rodeo et al. that show that BMP-2 did not induce the formation of cartilage at the attachment site. A comparison of the results of Rodeo et al. to the results presented in the specification show that the claimed composition induces an attachment of tendon to bone that is superior to that described by Rodeo et al. in that it more closely represents the natural ontogeny of this attachment.

Moreover, Applicants submit that the art does not teach that these particular components will function together to produce the result of a production of a connective tissue-cartilage-bone interface. For example, the specification shows that BMP-2 does not induce an ordered ring of bone formation around the periphery of a collagen sponge in a rat subcutaneous assay, nor, just interior, an ordered cartilage ring as compared to Bone Protein (Example 6A). Further, the specification shows that

TGFβ1 does not induce bone and cartilage formation *in vivo* (see Example 6B). Also, as discussed above, Rodeo et al. provide sufficient description to determine that BMP-2 alone does not induce the bone-cartilage-tendon interface produced by the claimed composition. BMP-3 and BMP-7 are considered to be osteogenic (i.e., bone inducing) proteins, similar to BMP-2. There is no teaching or suggestion in any art cited by the Examiner, nor in the known and demonstrated effects of the components, to indicate that they will, in the claimed combination, produce the specific attachment of tendon/ligament/cementum to bone with a formation of a fibrocartilage interface.

In summary, it is submitted that the Examiner has provided no teaching of the specific combination and amounts of proteins as claimed, but rather, an open-ended invitation to try any of a myriad of available growth factors and other proteins with no guidance that would lead one of skill in the art to choose the claimed composition or expect success. The issue is whether one of skill in the art would find it obvious to produce the claimed composition. Although the Examiner has indicated that the intended use does not give patentable weight to the composition *per se*, Applicants note that this is an obviousness rejection, and submit that the intended use is, nonetheless, a factor to be considered with regard to the motivation to make a given composition. The Examiner has not provided a reference that teaches the claimed composition, nor a combination of references that would suggest to or motivate one of skill in the art to choose the specifically claimed composition, and it would be clear to those of skill in the art that one can not simply put together *any* combination of different growth factors and expect to achieve the same result. Applicants have demonstrated through working examples that the claimed composition is capable of forming an attachment of tendon or ligament to bone that mimics the natural bone-fibrocartilage-connective tissue interface. Applicants have also demonstrated through working examples that neither BMP-2 nor TGFβ1 produce the same tissue formation when used singly. Finally, Applicants have explained in detail how the Rodeo et al. publication describes a different, inferior result than that obtained by the present inventors using the complex mixture of proteins as claimed (see October 26 response), and Applicants have explained why the combinations of references as a whole do not teach or suggest the claimed composition (see October 26 response).

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw all of the rejections under 35 U.S.C. § 103.

In the event that the Examiner has any questions regarding Applicants' position, the Examiner is respectfully requested to contact the below-named agent at (303)863-9700.

Respectfully submitted.

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